MINI-SYMPOSIUM

Rhythm control and cardioversion

N Sulke, F Sayers, G Y H Lip, on behalf of the Guideline Development Group for the NICE clinical guideline for the management of atrial fibrillation

Heart 2007;**93**:29–34. doi: 10.1136/hrt.2006.099879

The three main aims of treatment for paroxysmal atrial fibrillation are: (1) to suppress paroxysms of atrial fibrillation and maintain long-term sinus rhythm; (2) to control heart rate during paroxysms of atrial fibrillation if they occur; and (3) to prevent the complications associated with paroxysmal atrial fibrillation—that is, stroke and tachycardia-induced cardiomyopathy.[1]

Many patients with paroxysmal atrial fibrillation can be highly symptomatic, although asymptomatic paroxysms are common.[2] However, the abolition of symptoms of paroxysmal atrial fibrillation does not necessarily mean abolition of the atrial fibrillation per se, as heart rate slowing may abolish symptoms but still allow asymptomatic episodes to continue.[3] In some patients, it may be appropriate to document the frequency of arrhythmia by Holter monitoring or event recording. Of note, most pharmacological studies of paroxysmal atrial fibrillation have concentrated on the reduction of *symptomatic* recurrences of paroxysmal atrial fibrillation.

If attacks of paroxysmal atrial fibrillation are frequent, current clinical practice usually uses chronic prophylaxis with drugs to reduce the frequency of paroxysms after removal of precipitating factors such as caffeine, alcohol, stress, and adequate treatment of underlying diseases such as myocardial ischaemia, thyrotoxicosis, and heart failure.[1]

In the long term, few patients achieve complete suppression of paroxysms of atrial fibrillation. Drug treatment for paroxysmal atrial fibrillation may be administered as prophylaxis against recurrent atrial fibrillation, but in those patients who are asymptomatic or have rare paroxysms (eg, only a few paroxysms a year) may decide not to take routine medication or to use a ''pill-in-the-pocket'' strategy, and the patient's views need to be considered.

Based on the systematic review undertaken as part of this guideline development, propafenone appears to be at least as effective as sotalol in preventing the recurrence of atrial fibrillation for up to 12 months following administration,[4 5] although for longer periods propafenone may be more effective.[6] The two drugs were comparable in terms of side effects.[5] It was noted that class Ic agents (propafenone and flecainide) should be used with caution in patients with structural heart disease or coronary artery disease.

Amiodarone was found to be more effective than sotalol[7 8] and propafenone[9] in the prevention of recurrent atrial fibrillation. Due to concerns regarding contraindications of class Ic agents in patients with left ventricular dysfunction, amiodarone was regarded as the drug of choice in these patients with symptomatic paroxysms despite initial β-blocker treatment (fig 1).

The concerns over the long-term toxicity of amiodarone were not addressed in the evidence. Although the clinical evidence demonstrated that amiodarone was the most effective drug, its long-term use in patients with infrequent paroxysms needed to be fully weighed against the risk of side effects, especially since some (eg, lung fibrosis) could be serious. As an alternative to amiodarone, patients with paroxysmal atrial fibrillation could be considered for non-pharmacological approaches, such as pulmonary vein isolation.[10] However, the latter approach is not the magic cure, as illustrated by one recent study, where at the 6-month follow-up period, only 54% and 82% of patients remained free of arrhythmia-related symptoms after circumferential pulmonary vein ablation and after segmental pulmonary vein ablation, respectively.[11] Asymptomatic episodes may be significantly increased after catheter ablation, especially among previously symptomatic patients.[12]

Pill-in-pocket approach

In selected patients with recurrent paroxysmal atrial fibrillation, the out-of-hospital initiation of antiarrhythmic drugs may be possible, allowing for earlier treatment, a shorter duration of atrial fibrillation and a presumed likelihood of restoring and maintaining sinus rhythm. A pill-in-pocket approach is used in those not taking drugs regularly owing to infrequent symptoms or paroxysms, or taken as an extra drug dose in those already on a low maintenance of that particular drug.

The main concern with a pill-in-the-pocket approach is the risk of pro-arrhythmia often associated with antiarrhythmic drugs. Thus, this approach has generally been advocated only in those patients with a low risk of pro-arrhythmia and other adverse side effects. Such patients are typically those with no structural heart disease, absence of heart failure or left-ventricular dysfunction, and patients in whom there is evidence that the antiarrhythmic drug used has previously worked successfully with no adverse effects (eg, after at least one in-patient trial of the drug given as a single oral dose, under electrocardiographic monitoring).[13 14] The antiarrhythmic drugs amiodarone and propafenone have both been considered in several trials comparing the safety and efficacy of a single oral dose of the drug with the intravenous administration of the same drug.[15–18]

Treatment for paroxysmal atrial fibrillation should therefore be tailored to the patient. Patients with infrequent and brief paroxysms may be suitable for the pill in the pocket approach. However, for infrequent but protracted and symptomatic paroxysmal atrial fibrillation, rapid cardioversion of each event or antiarrhythmic drug prophylaxis may be considered. In cases where drug treatment is ineffective or not tolerated, referral for non-pharmacological approaches should be considered. Table 1 summarises the National Institute for Health and Clinical Excellence (NICE) guideline recommendations for the management of paroxysmal atrial fibrillation.

PERSISTENT ATRIAL FIBRILLATION

Currently, there are two main treatment strategies for persistent atrial fibrillation, a rate-control and a rhythm-control strategy. Rate control involves the use of chronotropic drugs or

Abbreviations: ECV, electrical cardioversion; PCV, pharmacological cardioversion; TOE, transoesophageal echocardiography

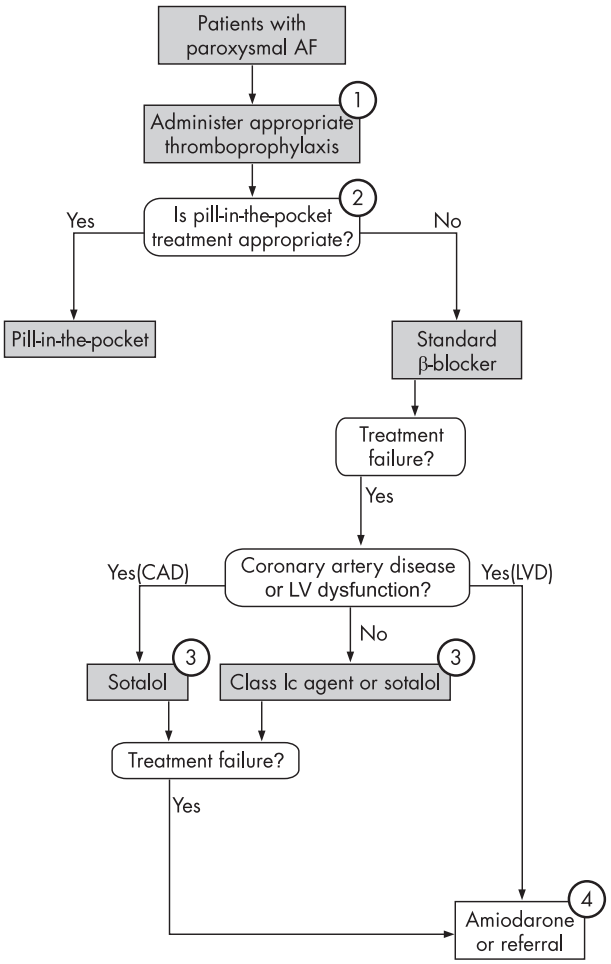

Figure 1 Management of paroxysmal atrial fibrillation (AF). (1) Based on stroke risk stratification algorithm. (2) A pill-in-the-pocket strategy should be considered in those who (a) have no history of left ventricular dysfunction, or valvular or ischaemic heart disease; (b) have a history of infrequent symptomatic episodes of paroxysmal AF; (c) have a systolic blood pressure >100 mm Hg and a resting heart rate >70 bpm; (d) are able to understand how to, and when to, take the medication. (3) Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily. (4) Referral for further specialist investigation should be considered, especially in those with lone AF or electrocardiogram evidence of an underlying electrophysiological disorder (eg, Wolff–Parkinson–White) or where pharmacological treatment has failed. CAD, coronary heart disease; LV, left ventricular; LVD, left ventricular dysfunction.

electrophysiological or surgical interventions to reduce the rapid heart rate (ventricular rate), which improves symptoms and potentially reduces the risk of associated morbidity.

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological or surgical interventions to convert the arrhythmia associated with atrial fibrillation to normal sinus rhythm. Patients who have been successfully cardioverted are generally given antiarrhythmic drugs for long term to help prevent the recurrence of atrial fibrillation. The rhythm-control strategies also require the appropriate administration of antithrombotic treatment to reduce the risk of occurrence of stroke and thromboembolic events.

Electrical versus pharmacological cardioversion

Cardioversion is performed as part of a rhythm-control treatment strategy, and if successful restores sinus rhythm. However, not all attempts at cardioversion are successful, and at 1 year after cardioversion approximately 50% of patients again contract atrial fibrillation.[19]

There are two types of cardioversion: electrical cardioversion (ECV) and pharmacological cardioversion (PCV). The optimal techniques and recommended protocols for performing cardioversion have been widely discussed in the literature.[20–22] Current clinical practice regards PCV as the preferred strategy in patients presenting with recent-onset atrial fibrillation (within 48 h); ECV is regarded as the preferred strategy when the atrial fibrillation is more prolonged.

Few studies have compared which patients would benefit most from ECV versus PCV. Two studies[23 24] failed to find any difference between these strategies when used as the initial treatment option. The evidence also failed to deal with many issues (ie, incidence of thromboembolism and stroke and improvements to quality of life). The choice of strategy was considered to be dependent on local facilities and available expertise. It was recognised that some clinicians perform elective cardioversion under general anaesthesia, whereas others performed the procedure under sedation.[25–27] Also, there has been a move towards nurse-led cardioversion services.[27–29] As the treatments were considered equally effective, highlighting patient choice was important. Informing patients that

Table 1 NICE guidelines for the management of paroxysmal atrial fibrillation

In patients with infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a ''no drug treatment'' strategy or a ''pill-in-the-pocket'' strategy should be considered and discussed with the patient
In patients with symptomatic paroxysms (with or without structural heart disease, including coronary artery disease), a standard β-blocker should be the initial treatment option

In patients with paroxysmal atrial fibrillation and no structural heart disease:
- where symptomatic suppression is not achieved with standard β-blockers, either
  –a class Ic agent (such as flecainide or propafenone), or
  –sotalol* should be given
- where symptomatic suppression is not achieved with standard β-blockers, class Ic agents or sotalol, either
  –amiodarone, or
  –referral for non-pharmacological intervention should be considered

In patients with paroxysmal atrial fibrillation and coronary artery disease:
- where standard β-blockers do not achieve symptomatic suppression, sotalol should be given
- where neither standard β-blockers nor sotalol achieve symptomatic suppression, consider either
  –amiodarone, or
  –referral for non-pharmacological intervention

In patients with paroxysmal atrial fibrillation with poor left-ventricular function:
- where standard β-blockers are administered as part of the routine management strategy and adequately suppress paroxysms, no further treatment is needed
- where standard β-blockers do not adequately suppress paroxysms, either
  –amiodarone, or
  –referral for non-pharmacological intervention should be considered

Patients on long-term medication for paroxysmal atrial fibrillation should be kept under review to assess the need for continued treatment and the development of any adverse effects

In patients with paroxysmal atrial fibrillation, a pill-in-the-pocket strategy should be considered in those who:
- have no history of left-ventricular dysfunction, or valvular or ischaemic heart disease; and
- have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation; and
- have a systolic blood pressure greater than >100 mm Hg and a resting heart rate above >70 bpm; and
- are able to understand how to, and when to, take the drugs

*Progressively titrated from 80 mg twice daily up to 240 mg twice daily.

Table 2 Cardioversion of patients with atrial fibrillation without haemodynamic instability

In patients with atrial fibrillation without haemodynamic instability in whom cardioversion is indicated:
- the advantages and disadvantages of both pharmacological (PCV) and electrical cardioversion (ECV) should be discussed with patients before initiating treatment
- where onset of atrial fibrillation was within 48 h previously, either PCV or ECV should be performed
- for those with more prolonged atrial fibrillation (onset >48 h previously), ECV should be the preferred initial treatment option

neither treatment has been shown to be more effective than the other is important and can help prevent disillusionment among patients when cardioversion fails.

Thus, the available evidence suggested PCV and ECV to be of comparable efficacies. However, it was believed that in more prolonged cases of atrial fibrillation electrical cardioversion is the preferred option based on clinical experience and current clinical practice. It was also considered preferable to attempt cardioversion as soon as possible after onset of atrial fibrillation, to maximise the likelihood of a successful outcome (table 2).

Pharmacological cardioversion

Clinical practice commonly uses Vaughan–Williams class Ia, Ic and III antiarrhythmic drugs for PCV.[22] However, these agents are associated with a risk of proarrhythmia in the presence of electrolyte abnormalities and ischaemic or structural heart disease.[30–32] This risk should be considered when choosing drugs for individual patients. Of note, the fast-acting intravenous β-blocker esmolol has also been used and shown to be effective.[33 34] Digoxin has been shown to be ineffective for use in PCV.[35–37]

Patients undergoing PCV are usually admitted to hospital and receive the antiarrhythmic drug intravenously, under electrocardiographic monitoring. These drugs may also be given orally, and have been shown to have comparable efficacies with intravenous administration at 24 h. For example, one study[38]—with a relatively small number of patients (n = 100)—suggested that class Ic drugs (flecainide and propafenone) are more effective than amiodarone at cardioverting patients with recent-onset atrial fibrillation at 2, 5 and 8 h after administration. However, at 24 h, the difference in efficacy disappeared, indicating that amiodarone had a longer period of onset than the class Ic drugs. This result is also consistent with all of the primary studies, with no study finding any significant difference in efficacy at ⩾24 h periods of observation. A separate, unblinded study[39] suggested that amiodarone and sotalol were comparable with each other for use in PCV in terms of both efficacy and safety.

The trials excluded patients with structural or functional heart disease (left ventricular dysfunction). There were concerns about the use of class I and class III antiarrhythmic drugs in these patients, although amiodarone was considered to be safe (table 3).

Table 3 Pharmacological cardioversion for patients with persistent atrial fibrillation

In patients with persistent atrial fibrillation, where the decision to perform pharmacological cardioversion using an intravenous antiarrhythmic agent has been made:
- In the absence of structural heart disease*, a class 1c drug (such as flecainide) should be the drug of choice
- In the presence of structural heart disease*, amiodarone should be the drug of choice

*Coronary artery disease or left-ventricular dysfunction.

ECV with concomitant antiarrhythmic drugs

In some cases, there is complete failure of ECV (complete shock failure or no conversion). In other cases, atrial fibrillation recurs within a few minutes after a short period of sinus rhythm (immediate recurrence); sometimes recurrence is delayed from 1 day to 2 weeks (subacute or early recurrence) and sometimes it occurs at beyond 2 weeks (late recurrence).[40]

Complete shock failure and immediate recurrence are estimated to occur in approximately 25% of patients undergoing ECV, and subacute or early recurrences occur within 2 weeks in another 25%.[40] The concomitant administration of antiarrhythmic drugs is perceived to increase the likelihood of successful cardioversion and the maintenance of sinus rhythm after cardioversion, and this section delineates the evidence for this.

Amiodarone and sotalol generally increased the likelihood of a successful cardioversion in comparison with the control drug.[41–44] The historical literature regarding the amount of energy delivered during ECV were not considered to reflect current practice, as these studies administered a low-energy level shock and then escalated to a higher energy level shock. Therefore, it was unclear whether the administration of antiarrhythmic drugs decreased the energy requirement for successful cardioversion. Furthermore, biphasic defibrillators (which deliver lower energy shocks) are increasingly used in UK.

From the limited data available for small patient numbers, there was supporting evidence for the use of amiodarone, sotalol and, possibly, propafenone in reducing the recurrences of atrial fibrillation after cardioversion (fig 2). None of the evidence reflected concerns regarding the potential adverse effects of antiarrhythmic drugs such as amiodarone. It was therefore not considered appropriate to recommend these drugs for routine ECV, although they may be beneficial in cases with a perceived increased risk of unsuccessful electrical cardioversion (eg, long duration of atrial fibrillation; table 4).

Antiarrhythmic drugs to maintain sinus rhythm

In persistent atrial fibrillation, antiarrhythmic drugs are prescribed to increase the likelihood of maintaining sinus rhythm after successful ECV or PCV.

In the UK, prophylactic drug treatment is not usually used in cases of a first-detected episode of atrial fibrillation, especially if atrial fibrillation is secondary to a precipitant that has since been corrected. Without antiarrhythmic drugs, the recurrence rate is high. Clinical studies have shown the efficacy of various antiarrhythmic drugs (amiodarone, propafenone, disopyramide, sotalol, flecainide, quinidine and azimilide) against no treatment, placebo or digoxin.[22 45] It is clear from these trials that the use of antiarrhythmic drugs improves the maintenance of sinus rhythm after cardioversion, but even despite treatment, relapse to atrial fibrillation occurs in approximately 50% at 12 months. Moreover, the need for antiarrhythmic drugs has to be balanced against adverse effects and a higher mortality in some patients[46] (fig 3, table 5).

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY-GUIDED CARDIOVERSION

Cardioversion of atrial fibrillation is associated with an increased risk of stroke and thromboembolism. To minimise this risk, anticoagulation is conventionally recommended for a minimum of 3 weeks before, during, and for a minimum of 4 weeks after cardioversion. Even when precardioversion transoesophageal echocardiography (TOE) fails to show left atrial thrombus, some patients have a thromboembolism after

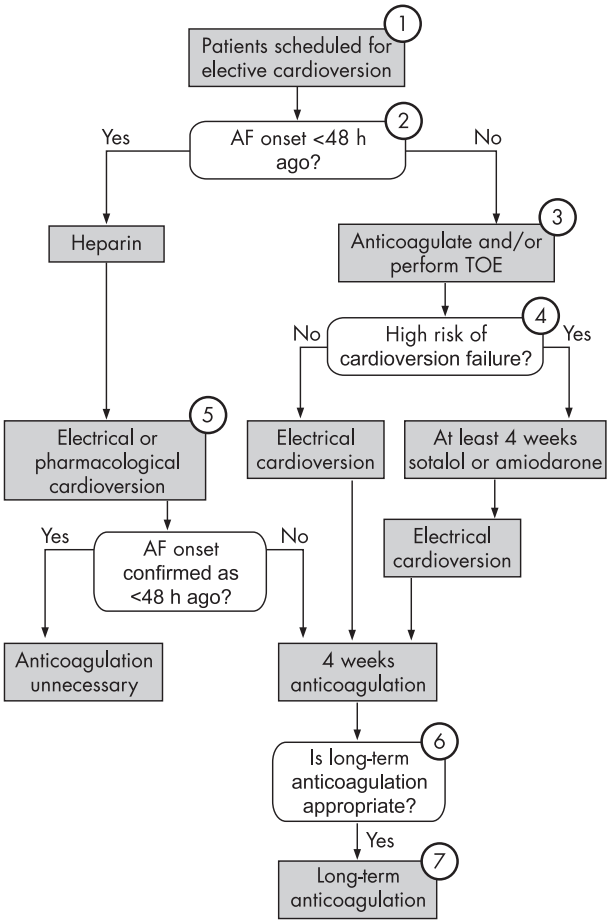

Figure 2 Cardioversion treatment algorithm. (1) Perform transthoracic echocardiograph (TTE) examination before rhythm-control treatment strategy involving cardioversion. (2) Also consider patient preference after a discussion of the advantages and disadvantages of each option. (3) Administer therapeutic anticoagulation for at least 3 weeks before transoesophageal echocardiogram (TOE)-guided cardioversion, depending on preference, contraindications and practicalities. (4) High risk of cardioversion failure suggested by previous failure of recurrence of atrial fibrillation (AF). (5) Intravenous amiodarone as drug of choice in those with structural heart disease; flecainide in those without structural heart disease. (6) As determined by the stroke risk stratification algorithm or where there is a high risk of recurrence of AF. Patients with a history of AF of >12 months, mitral valve disease, left ventricular dysfunction, enlarged left atrium and a history of recurrence of AF are at a higher risk of recurrence of AF. (7) Anticoagulation should be given to a target international normalised ratio (INR) of 2.5 (range 2–3).

Table 4 Drugs to facilitate electrical cardioversion in patients with atrial fibrillation

When patients with atrial fibrillation are to undergo elective electrical cardioversion and there is cause for heightened concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of atrial fibrillation), concomitant amiodarone or sotalol* should be given for at least 4 weeks before the cardioversion

*To be progressively titrated from 80 mg twice daily up to 240 mg twice daily.

cardioversion (especially if no anticoagulation has been given).[22]

As it may take some time to achieve therapeutic international normalised ratio for three consecutive weeks, some patients may wait for months before cardioversion is attempted. As it is perceived that patients are more likely to successfully cardiovert the shorter the time they have been in atrial fibrillation, strategies to facilitate early cardioversion have been explored.

One strategy is TOE-guided cardioversion, where a patient with atrial fibrillation of >48 h duration undergoes a TOE to assess for intracardiac thrombus. In the absence of thrombus, heparin is usually given and cardioversion is performed. Anticoagulation with warfarin is subsequently continued for a minimum of 4 weeks. Patients in whom a thrombus is

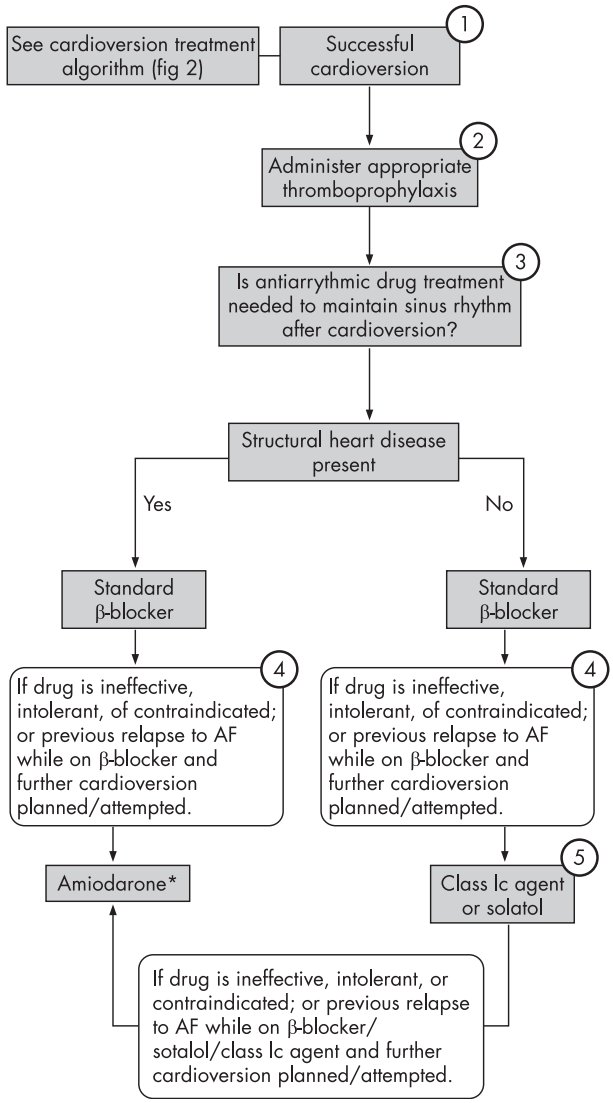

Figure 3 Rhythm-control treatment algorithm for persistent atrial fibrillation (AF). *If rhythm control fails, consider the patient for rate-control strategy or specialist referral in those with lone AF or electrocardiogram evidence of underlying electrophysiological disorder (eg, Wolff–Parkinson–White syndrome). (1) Patients with persistent AF who have been selected for a rhythm-control treatment strategy. (2) Based on stroke risk stratification algorithm and cardioversion treatment algorithm. (3) An antiarrhythmic drug is not required to maintain sinus rhythm for those patients in whom a precipitant (such as chest infection, fever, etc) has been corrected and cardioversion has been successfully performed. (4) Routine follow-up to assess the maintenance of sinus rhythm should take place at 1 and 6 months after cardioversion. Any patients found at follow-up to have relapsed back into AF should be fully re-evaluated for a rate-control or a rhythm-control strategy*. (5) Class I_c agents include flecainide and propafenone. Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily. TOE, transoesophageal echocardiography.

Table 5 Maintaining sinus rhythm in patients with persistent atrial fibrillation

An antiarrhythmic drug is not required to maintain sinus rhythm in patients with persistent atrial fibrillation in whom a precipitant (such as chest infection, fever) has been corrected and cardioversion has been performed successfully, provided there are no risk factors for recurrence.
In patients with persistent atrial fibrillation who require antiarrhythmic drugs to maintain sinus rhythm and who have structural heart disease:
- a standard β-blocker should be the initial treatment option
- where a standard β-blocker is ineffective, contraindicated or not tolerated, amiodarone should be used

In patients with persistent atrial fibrillation who require antiarrhythmic drugs to maintain sinus rhythm and who do not have structural heart disease:
- a standard β-blocker should be the initial treatment option
- where a standard β-blocker is ineffective
  –a class Ic agent
  –or sotalol* should be given
- where other drug classes are ineffective, contraindicated or not tolerated, amiodarone should be given

*Progressively titrated from 80 mg twice daily up to 240 mg twice daily.

identified by TOE are considered to be at high risk of thromboembolism after cardioversion, and are usually treated with conventional therapeutic anticoagulation for at least 3–4 weeks before the TOE is repeated (fig 4).

Overall, the clinical studies suggest that TOE-guided cardioversion has efficacy comparable to conventional strategy.[47 48] Although bleeding was reduced in the TOE-guided strategy, this was perceived to be a result of the lesser time spent on anticoagulation, and therefore TOE-guided cardioversion could be deemed preferable in patients with an increased bleeding risk. The health economic studies suggested that TOE-guided cardioversion may be a cost-effective treatment strategy.

The theoretical advantage of early cardioversion being more likely to be successful was not supported by the current clinical trial data. Nonetheless, the studies were underpowered to detect major differences in this, and in mortality and embolic event rates. TOE-guided cardioversion was considered a specialised procedure requiring adequately experienced staff and appropriate facilities. TOE-guided cardioversion should be an available treatment, as some patients would prefer the option of not undergoing prolonged anticoagulation, or where a minimal period of precardioversion anticoagulation is indicated due to patient choice or bleeding risks.

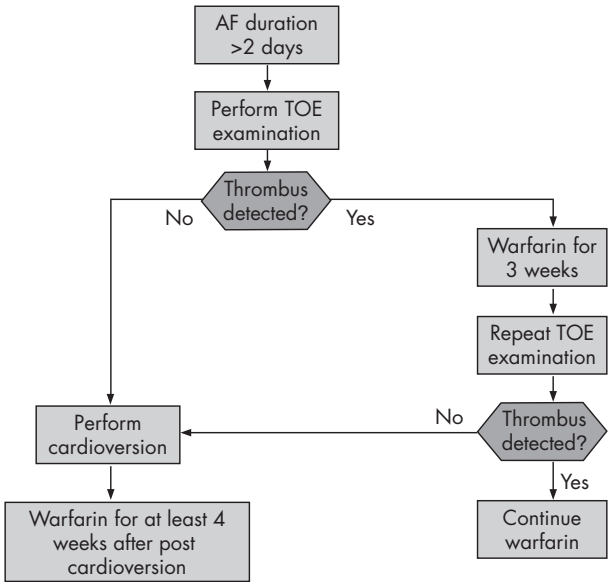

Figure 4 Cardioversion with transoesophageal echocardiography (TOE)-guided strategy. AF, atrial fibrillation.

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Competing interests: None declared.

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Published Online First 7 September 2006

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IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2006.093773

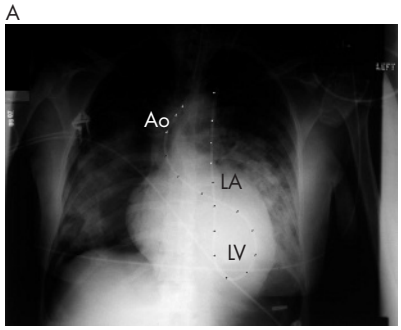
Brain abscess associated with an unusual cause of right to left shunt

A 33-year-old woman with a history of brain abscess 4 years earlier was admitted with an infected cranial bone flap requiring surgical debridement. Four days postoperatively she was found collapsed, presumed secondary to a seizure. She was resuscitated but developed severe aspiration pneumonia. Systemic pressures were recorded from a left internal jugular line, and a chest *x* ray (panel A) suggested that it had passed via a persistent left superior vena cava (SVC) into the left atrium and ventricle and into the ascending aorta. The diagnosis was confirmed by echocardiography: intravenous agitated saline contrast from the left arm showed immediate opacification of the left heart (panel B). She died from multiorgan failure 24 h later. Postmortem examination confirmed this isolated anomaly.

Right to left shunts predispose to cerebral abscess. A left SVC draining directly to the left atrium is a rare cause of right to left shunt (<5:100 000 of the general population).

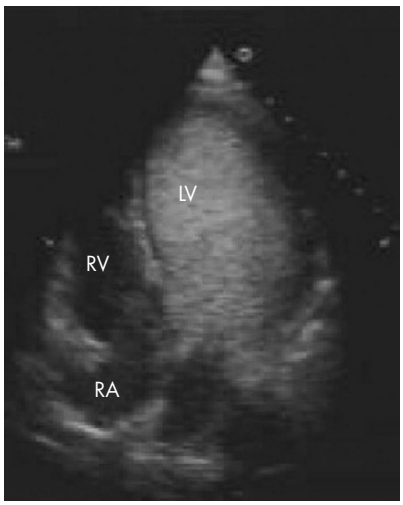
This case highlights two very important clinical issues. Firstly, a brain abscess in the absence of an obvious precipitating cause should prompt a search for a right to left shunt with saline contrast echocardiography. Secondly, saline contrast studies should be performed from the left and not the right arm, to prevent overlooking a persistent left SVC to left atrium communication.

A



Anteroposterior chest *x* ray showing central venous catheter (dotted line) emerging from the left internal jugular vein/persistent left superior vena cava, entering the left atrium, looping in the left ventricle with the tip in the ascending aorta. Ao, aorta; LA, left atrium; LV, left ventricle.

B



Transthoracic echocardiography-modified apical four-chamber view showing dense left ventricle opacification only (white) following left arm intravenous agitated saline injection. LV, left ventricle, RA, right atrium; RV, right ventricle.

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Competing interests: None.